Conflict of Interest and Clinical Re$earch:

NIH Dept. of Clinical Bioethics Seminar

May 18, 2005

Cary P. Gross, M.D.

Yale University School of Medicine

Robert Wood Johnson Clinical Scholars Program

Disclosure

- Research Support: Boehringer-Ingelheim

Disclosure

- Research Support: Boehringer-Ingelheim

Use Plavix

Disclosure

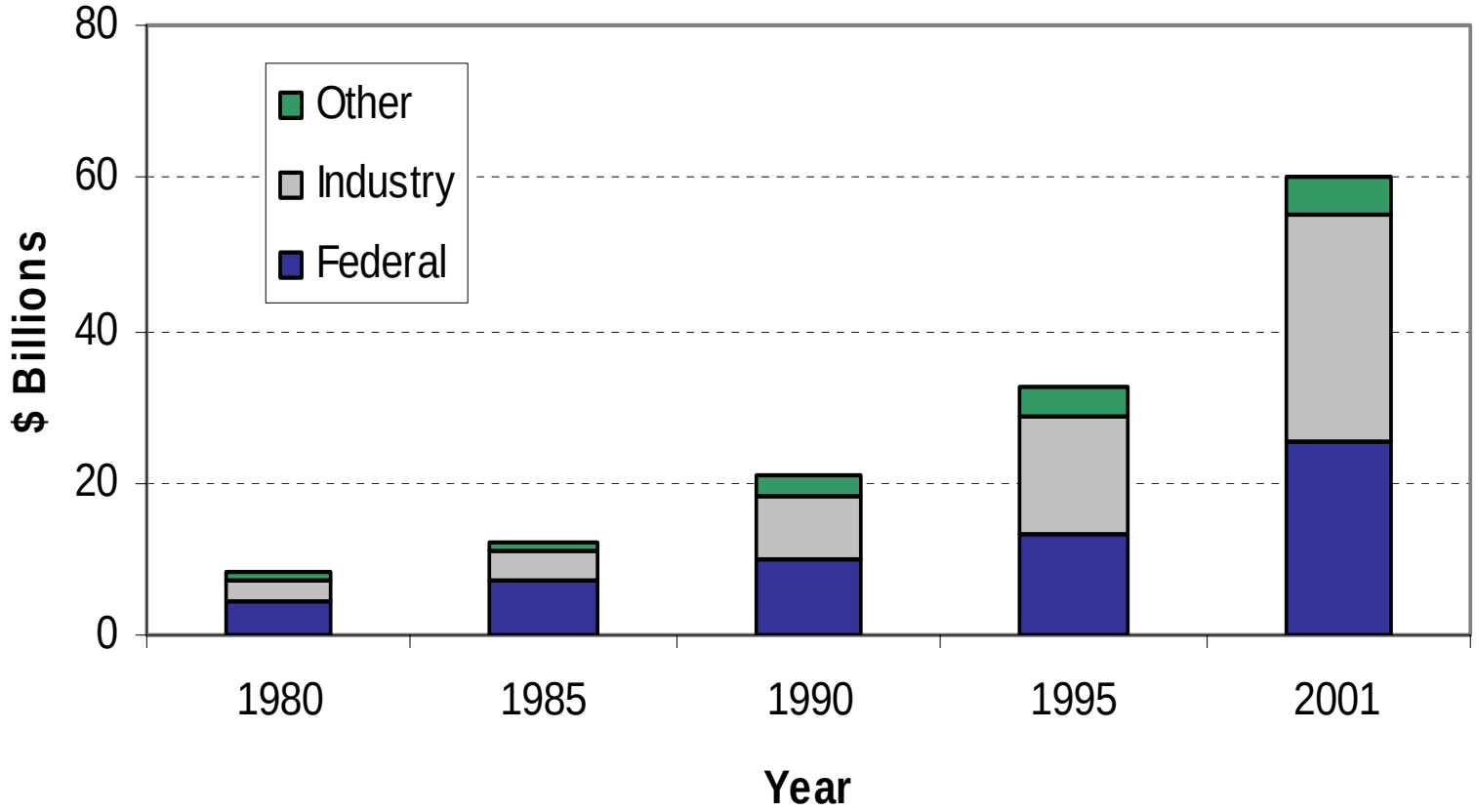
- Research Support: Boehringer-Ingelheim

Conflict of Interest and Clinical Research Objectives

- Evolution of the medical research landscape
- How financial conflicts bias science, scientists, and institutions
- Repairing the system

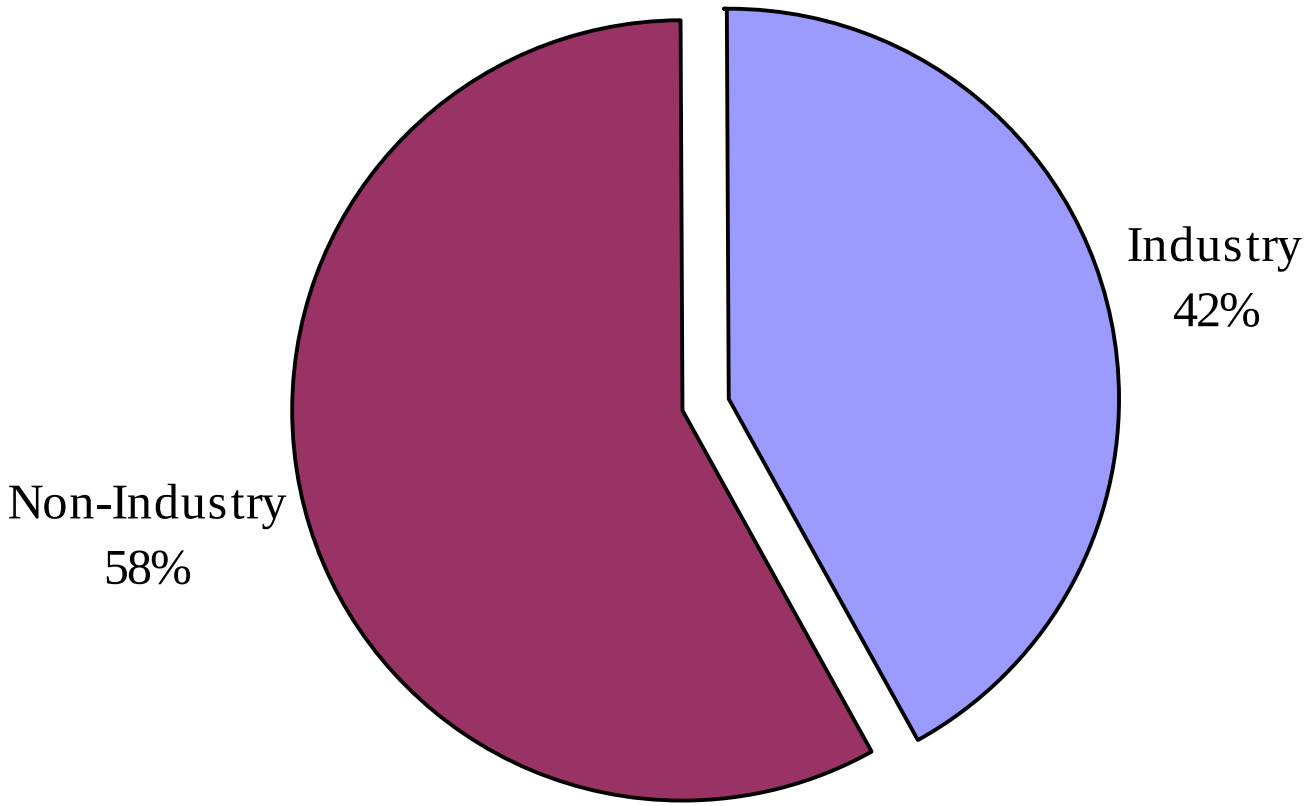
I - Evolution of the Research Landscape

National Biomedical Research Expenditures



Source: PhRMA Industry Profile 2004; NIH Office of the Director; NSF,2000

Sponsorship of published RCTs



Gross et al. *BMJ*, 2002.

Prevalence of financial conflicts

- 22% of community internists participated in industry trials in 2003
- 28% of faculty received industry research funds (1996)
- 124 academic institutions held equity in businesses engaged in research at the same institution

Ashar et al. *JGIM*, 2004.

Blumenthal et al. *N Eng J Med*. 1996

Industry and the FDA

- Prescription Drug User Fee Act (1992)
  - Goal is to speed approval process
  - Industry $  FDA

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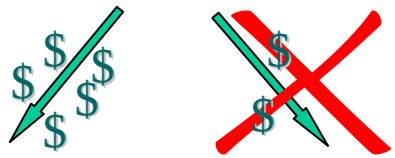
  - Industry $ → FDA



Premarketing evaluation

- RCTs
  - Thousands of patients
  - Months of use
- "Demonstrated Benefits vs. Known Risks"

Postmarketing surveillance

- Real world
  - Millions of patients
  - Years of Use
- Actual Benefits vs. Risks

Part I: Summary

- Research is a commodity
- More drugs, less scrutiny
- Increased consumer demand

Financial Conflict of Interest

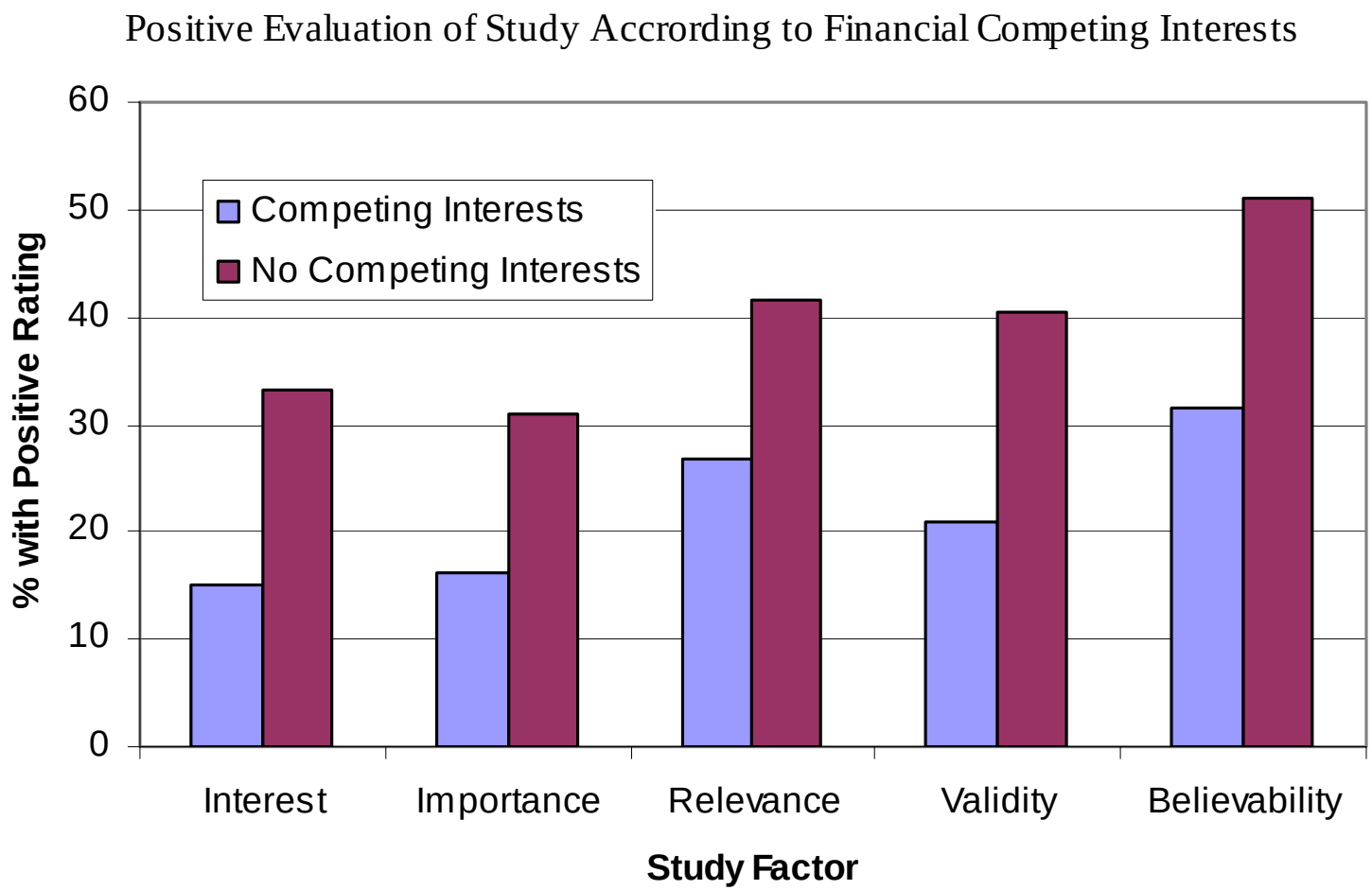
"Situations in which financial considerations may compromise, or have the appearance of compromising, an investigator's judgement in conducting or reporting research."

1990 AAMC Guidelines

Non-Financial CoIs

- Financial
  - Study support
  - Investigator support to conduct a study
  - Other:
    - Royalties/patents
    - Expert Witness
    - “Insider” Information
- Non-financial
  - Desire to prove prior hypotheses were correct
  - Self-promotion/peer recognition
  - Political agendas
  - Religious beliefs

Clinicians are concerned about COI



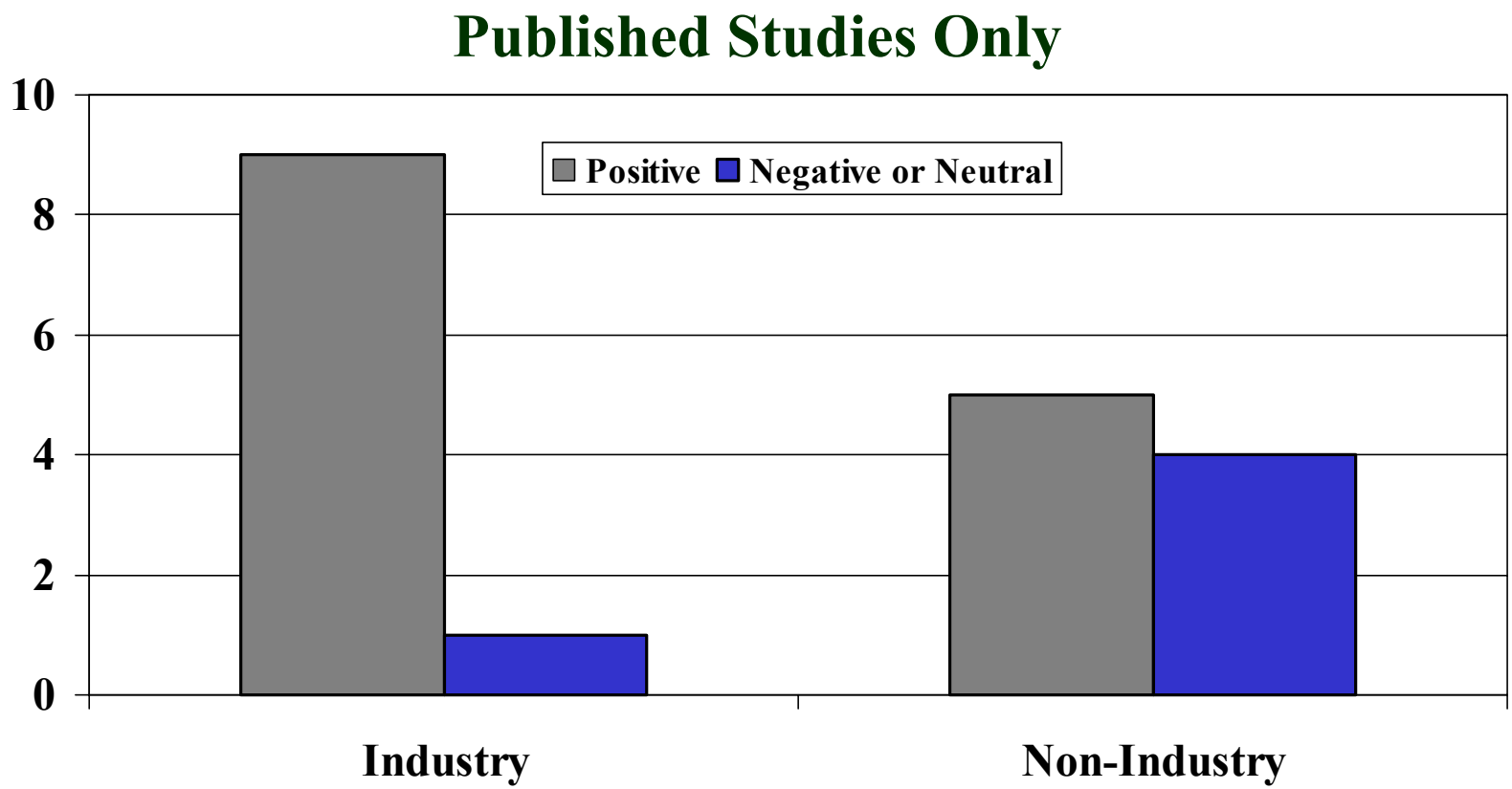
Chaudry S. BMJ. *2002; 325: 1391*

Prospective Trial Participants are concerned about COI

	Heart Disease	**Breast Cancer**	**Depression**
Want to know financial arrangement	58%	69%	56%
Want researcher's information on informed consent form	68%	74%	64%
If researcher has financial interest, patient is less inclined to participate	22%	31%	28%

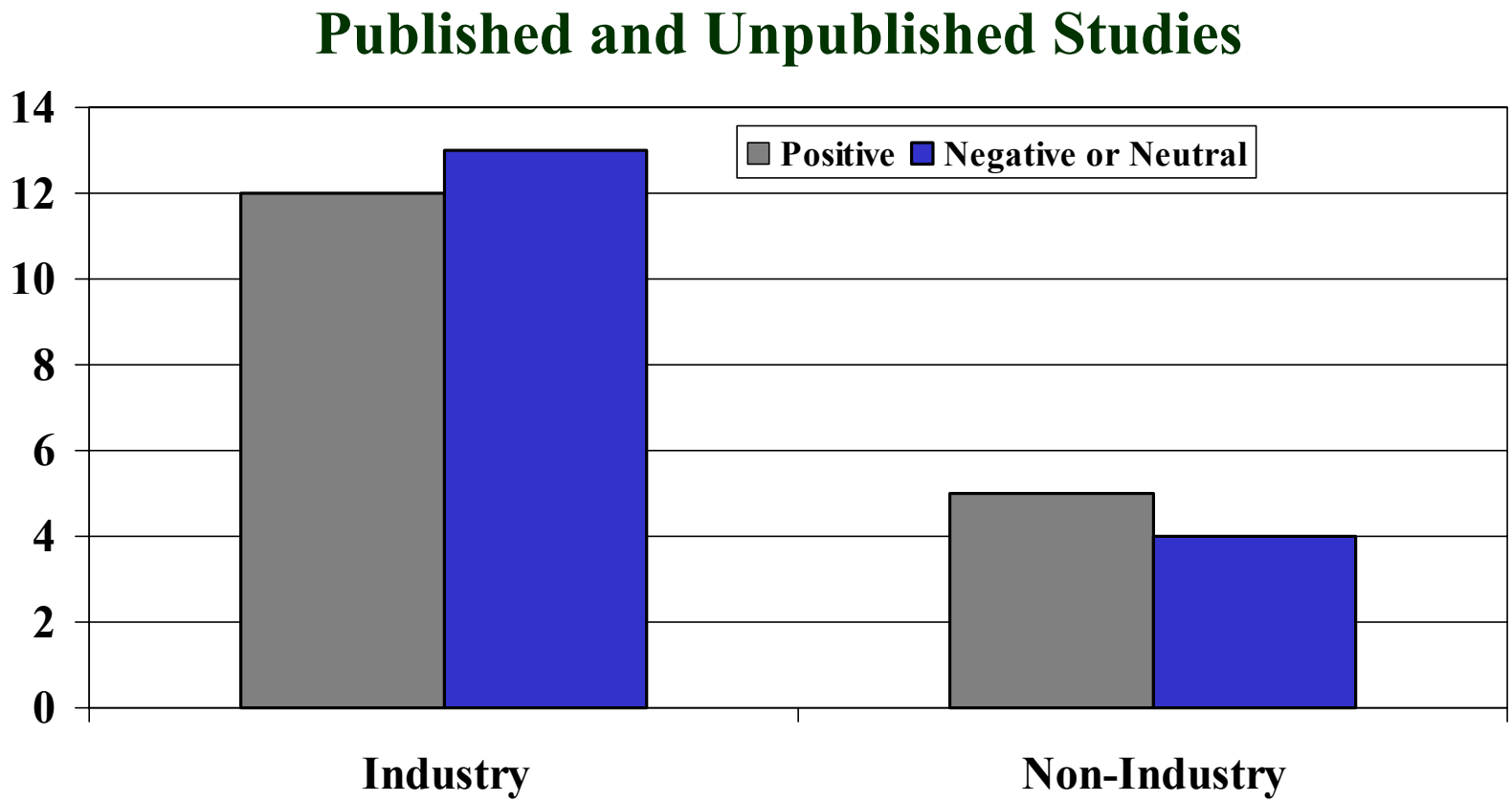
II - How COI Can Promote Bias

Suppressing dissemination of evidence: SSRI RCTs in Children



Source: Goozner et al, Center for Science in the Public Interest, 2004

Suppressing dissemination of evidence: SSRI vs. Placebo in Children



Source: Goozner et al, Center for Science in the Public Interest, 2004

Bayer and Cerivastatin

- July 1999 trial data:
  - High Dose Cerivastatin ⟶ CPK ⇈ in 12%
  - No further study of high dose cerivastatin

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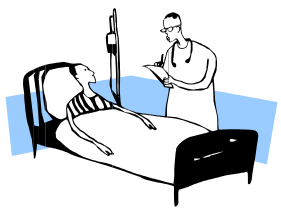
  - High Dose Cerivastatin ⟶ CPK ⇈ in 12%
  - No further study of high dose cerivastatin
- August 1999 Bayer internal document:

  "*The large percentage of patients experiencing CK elevations led to a consensus not to publish the results of this study*"

Bench to Bedside

Data Analysis
& Interpretation

Scientific Evidence



Celecoxib

Long-term

Arthritis

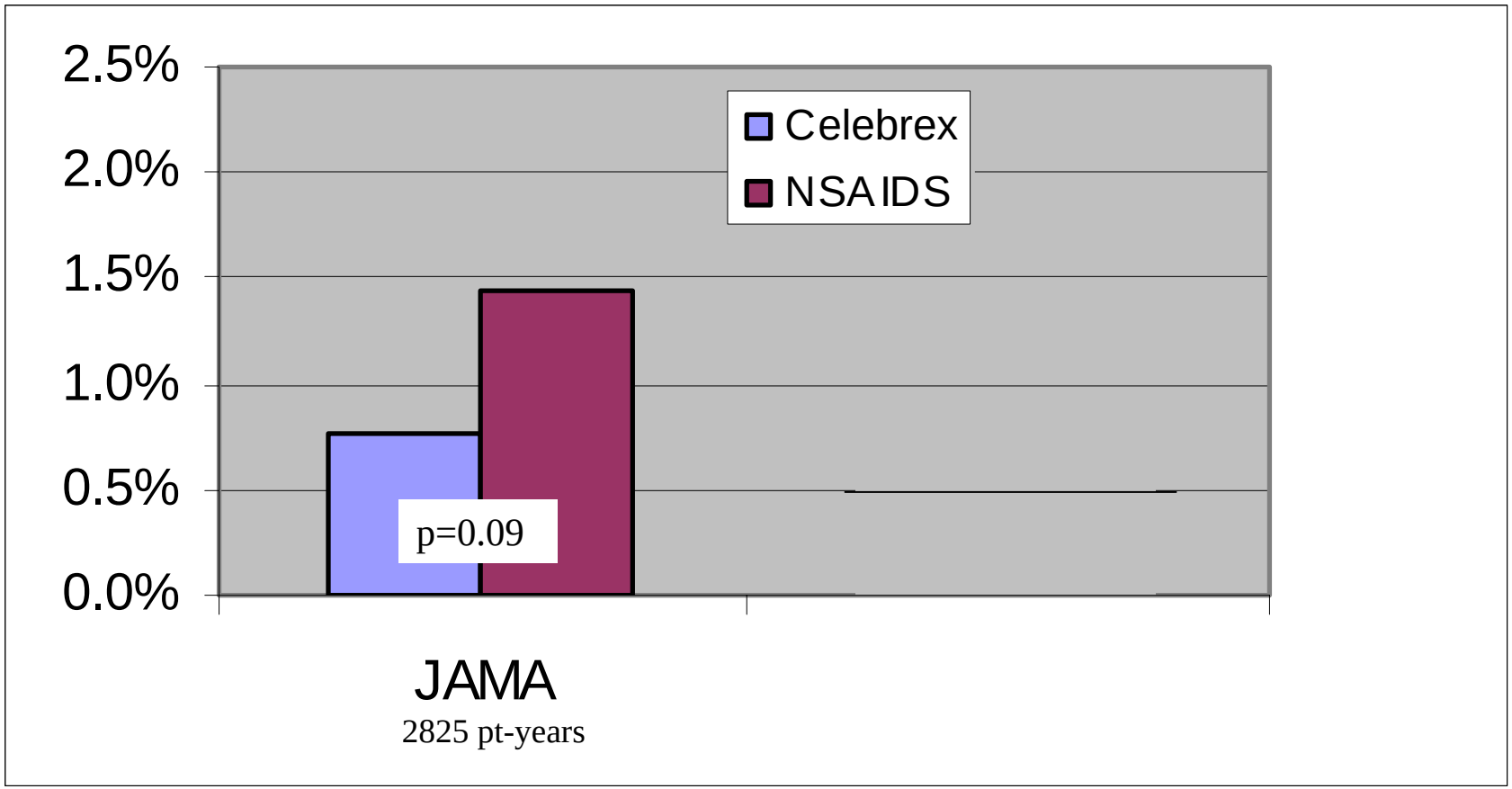
Safety

Study

CLASS Design

- RCT
- Celecoxib Vs. NSAIDS
- 1° Endpoint: Complicated Ulcer

CLASS Study: Incidence of ulcer complications at 6 months



Sources: Silverstein et al, JAMA; 2000; 284; 1247-55
FDA Arthritis Advisory Panel, February 7, 2001

Study Conclusions in JAMA

Manuscript:

"Celecoxib associated with lower incidence of symptomatic and ulcer complications combined"

Silverstein et al, JAMA; 2000; 284; 1247-55

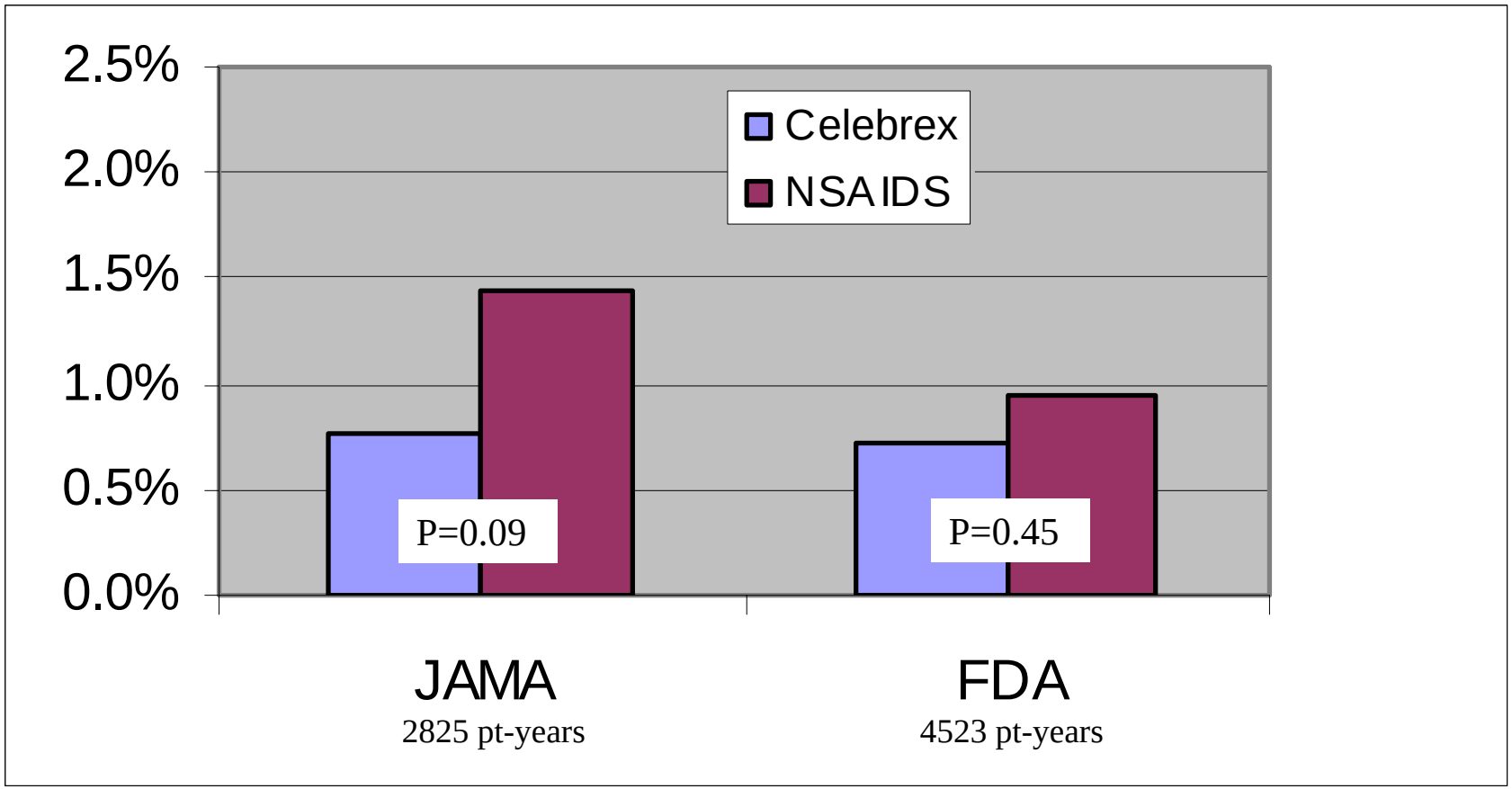
Editorial:

"….suggests that Celecoxib is effective at reducing the risk of symptomatic ulcers…..However, because this prospective analysis was limited to six months, careful future analysis will be required…."

M Wolfe, JAMA; 2000; 284; 1297-9

CLASS Study:

JAMA 6 month vs. complete 12 month follow-up



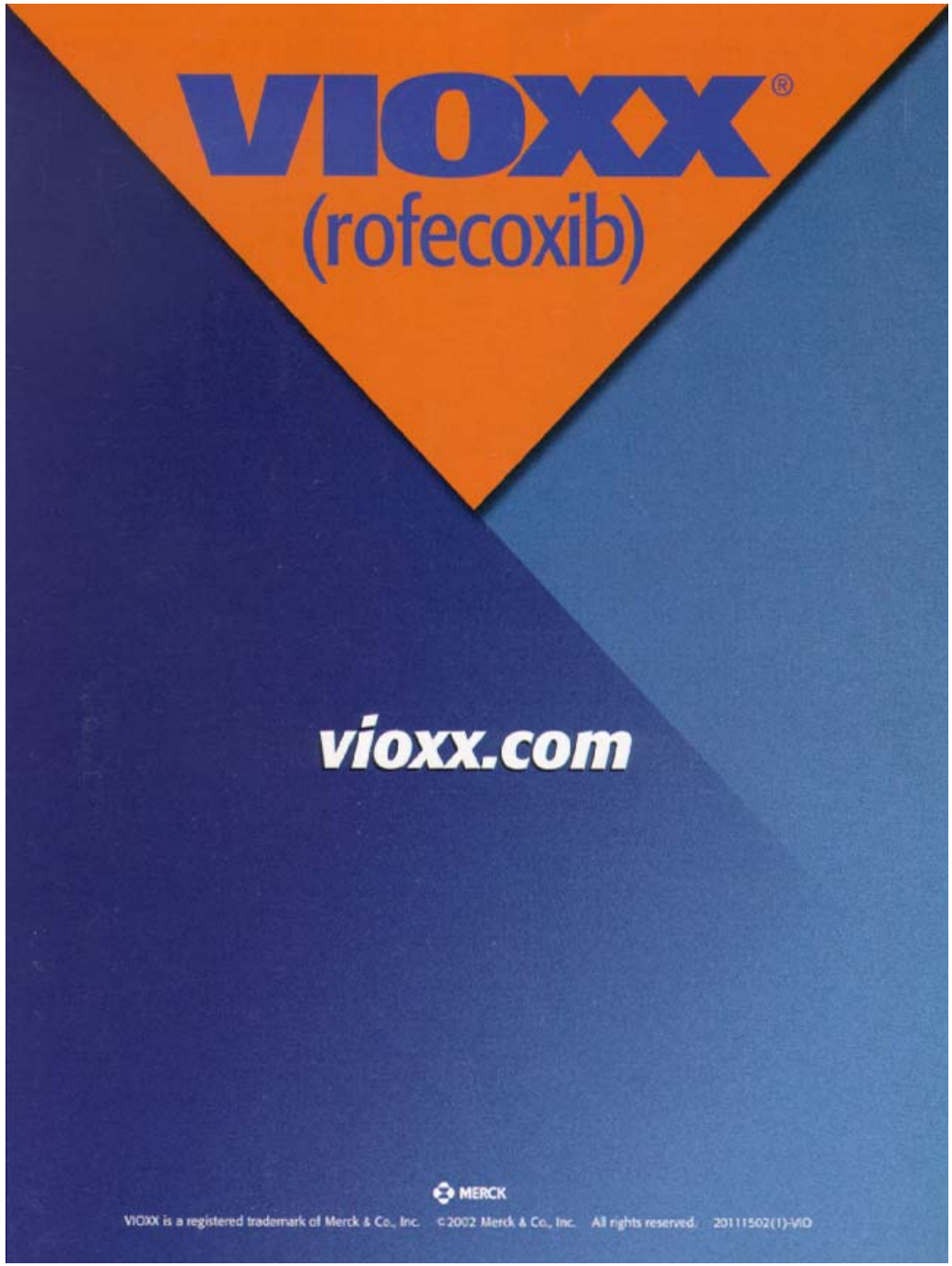
Sources: Silverstein et al, JAMA; 2000; 284; 1247-55
FDA Arthritis Advisory Panel, February 7, 2001

"I am furious…I wrote the editorial. I looked like a fool - but all I had available to me was the data presented in the article."

M Wolfe, Washington Post, August 2001

"We are functioning on a level of trust that was….broken."

C. DeAngelis, Washington Post, August 2001


VIOXX®
(rofecoxib)
vioxx.com
MERCK
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COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

Background Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal antiinflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods We randomly assigned 8076 patients who were at least 50 years of age (or at least 40 years of age and receiving long-term glucocorticoid therapy) and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers).

Results Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; $P<0.001$). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; $P=0.005$). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

Conclusions In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.)

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are among the most commonly used medications in the world.[1] A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs,[2] the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.[3,4]

Most NSAIDs inhibit both cyclooxygenase-1 and cyclooxygenase-2, isoenzymes involved in the synthesis of prostaglandins.[5] Cyclooxygenase-1 is constitutively expressed and generates prostanoids involved in the maintenance of the integrity of gastrointestinal mucosa and platelet aggregation,[6] whereas at sites of inflammation, cyclooxygenase-2 is induced to generate prostaglandins that mediate inflammation and pain.[7] The antiinflammatory effects of nonselective NSAIDs (those that inhibit both cyclooxygenase-1 and cyclooxygenase-2) therefore appear to be mediated through the inhibition of cyclooxygenase-2,[8] whereas their harmful effects in the gastrointestinal tract as well as their antiplatelet effects are believed to occur primarily through the inhibition of cyclooxygenase-1.[5]

Agents that selectively inhibit cyclooxygenase-2 have antiinflammatory and analgesic effects that are simi-

From the Institute for Work and Health, Mount Sinai Hospital, and the University Health Network, Toronto (C.B.); the Gastrointestinal Division, Department of Medicine, University of Southern California School of Medicine, Los Angeles (L.L.); Merck, Rahway, N.J. (A.R., D.S.); the Faculty of Medicine and Research Division, Universidad Nacional Autonoma de Mexico, and Hospital General de Mexico, Mexico City, Mexico (R.B.-V.); University of Texas–Houston School of Public Health, Houston (B.D.); the Department of Clinical Pharmacology, University of New South Wales and St. Vincent's Hospital, Sydney, Australia (R.D.); the Division of Rheumatology, Department of Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil (M.B.F.); the Division of Gastroenterology, School of Medical and Surgical Sciences, University Hospital, Nottingham, United Kingdom (C.J.H.); the Division of Rheumatology and Clinical Immunology, University of Maryland, Baltimore (M.C.H.); Oslo City Department of Rheumatology, and Diakonhjemmet Hospital, Oslo, Norway (T.K.K.); and the Office of Clinical Research and Training, Northwestern University School of Medicine, Chicago (T.J.S.). Address reprint requests to Dr. Bombardier at the Institute for Work and Health, 250 Bloor St. E., Suite 702, Toronto, ON M4W 1E6, Canada, or at claire.bombardier@utoronto.ca.

Arthur Weaver, M.D., Arthritis Center of Nebraska, Lincoln, was another author.

VIGOR results:

vigorously reported?

Outcome (9-months f/u)	Rofecoxib (n=4,047)	Naproxen (n=4,029)	Relative Risk	P-value
Arthritis Disability Score Δ	-0.11	-0.12	-	NS
GI Bleeds*				
Total	2.1	4.5	0.5	<0.001
Complicated	0.6	1.4	0.4	0.005
Myocardial Infarction	0.4%	0.1%	4.0	<0.05

** (per 100 pt-year)*

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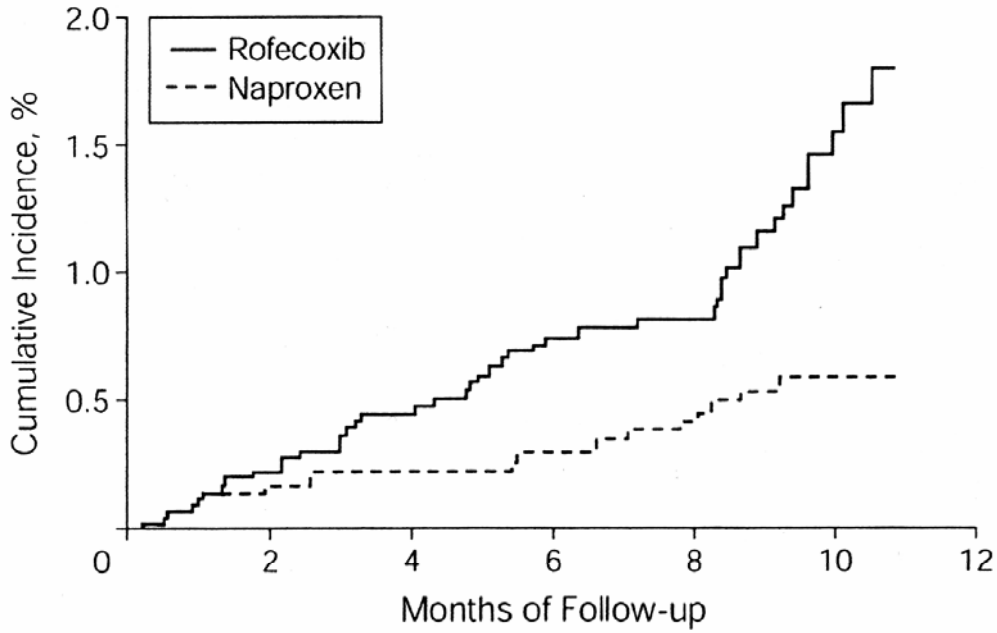
Figure 1. Time to Cardiovascular Adverse Event in the VIGOR Trial



No. at Risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

Relative risk (95% confidence interval) = 2.38 (1.39-4.00); $P<.001$. VIGOR indicates Vioxx Gastrointestinal Outcomes Research.

Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib

Marvin A. Konstam, MD; Matthew R. Weir, MD; Alise Reicin, MD; Deborah Shapiro, DrPh; Rhoda S. Sperling, MD; Eliav Barr, MD; Barry J. Gertz, MD, PhD

Background—In comparing aspirin, nonselective nonsteroidal antiinflammatory agents (NSAIDs), and cyclooxygenase (COX)-2 inhibitors, variation in platelet inhibitory effects exists that may be associated with differential risks of cardiovascular (CV) thrombotic events. Among the randomized, controlled trials with the COX-2 inhibitor rofecoxib, one study demonstrated a significant difference between rofecoxib and its NSAID comparator (naproxen) in the risk of CV thrombotic events. A combined analysis of individual patient data was undertaken to determine whether there was an excess of CV thrombotic events in patients treated with rofecoxib compared with those treated with placebo or nonselective NSAIDs.

Methods and Results—CV thrombotic events were assessed across 23 phase IIb to V rofecoxib studies. Comparisons were made between patients taking rofecoxib and those taking either placebo, naproxen (an NSAID with near-complete inhibition of platelet function throughout its dosing interval), or another nonselective NSAIDs used in the development program (diclofenac, ibuprofen, and nabumetone). The major outcome measure was the combined end point used by the Antiplatelet Trialists' Collaboration, which includes CV, hemorrhagic, and unknown deaths; nonfatal myocardial infarctions; and nonfatal strokes. More than 28 000 patients, representing >14 000 patient-years at risk, were analyzed. The relative risk for an end point was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib with placebo; 0.79 (95% CI: 0.40, 1.55) when comparing rofecoxib with non-naproxen NSAIDs; and 1.69 (95% CI: 1.07, 2.69) when comparing rofecoxib with naproxen.

Conclusions—This analysis provides no evidence for an excess of CV events for rofecoxib relative to either placebo or the non-naproxen NSAIDs that were studied. Differences observed between rofecoxib and naproxen are likely the result of the antiplatelet effects of the latter agent. **(*Circulation*. 2001;104:2280-2288.)**

Key Words: rofecoxib ■ anti-inflammatory agents, nonsteroidal ■ cardiovascular diseases ■ thrombosis

Nonselective, nonsteroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, diclofenac, nabumetone, naproxen, indomethacin, and aspirin inhibit both cyclooxygenase isoforms (COX-1 and COX-2) over their clinical dose range.[1] In contrast, rofecoxib is highly selective for only the COX-2 isoform over its clinical dose range.[2,3] In the gastrointestinal system, nonselective NSAIDs have been associated with gastroduodenal mucosal injury, whereas selective COX-2 inhibitors have demonstrated improved gastrointestinal safety and tolerability.[4–10] COX-1 inhibition has been associated with decreased synthesis of platelet-derived thromboxane, a vasoconstrictor and potent inducer of platelet aggregation.[11]

In comparing aspirin, nonselective NSAIDs, and COX-2 inhibitors, variation in platelet inhibitory effects may result in different influences on the rates of cardiovascular (CV) thrombotic events.[11] Sustained inhibition of COX-1–mediated thromboxane synthesis underlies the efficacy of aspirin in significantly reducing the incidence of CV death, myocardial infarction (MI), and stroke in high-risk patients.[11–14] Aspirin produces irreversible inhibition of platelet COX-1: this inhibition is near-complete and is sustained for at least 48 hours after a single dose.[14] In contrast to aspirin, nonselective NSAIDs are reversible inhibitors of COX-1: the extent and duration of inhibition closely follows their potency and systemic plasma drug concentrations, and the effect is reversible as a function of drug elimination.[14] Some evidence suggests that nonselective NSAIDs that mediate near-complete inhibition of platelet function throughout their entire dosing interval may be similar to aspirin and also

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Drs Konstam and Weir have been paid consultants to Merck and Co and Pharmacia, and Dr Konstam also has been a paid consultant to Pfizer Inc. Neither has been compensated for work on this article. Drs Reicin, Shapiro, Sperling, Barr, and Gertz are employees of Merck Research Laboratories, Merck and Co, Inc. As such, they receive financial compensation that includes stock ownership and stock options.

This article originally appeared Online on October 15, 2001 (*Circulation*. 2001;104:r15–r23).

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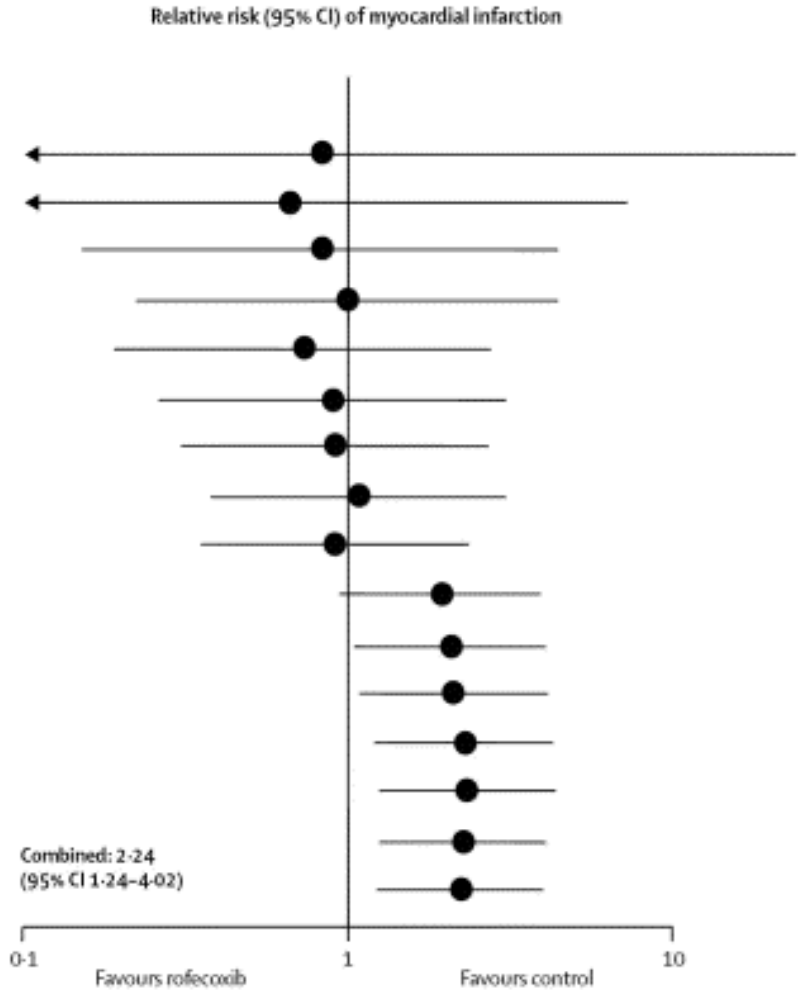
***Circulation* is available at http://www.circulationaha.org**

Risk of cardiovascular events: cumulative meta-analysis

Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007



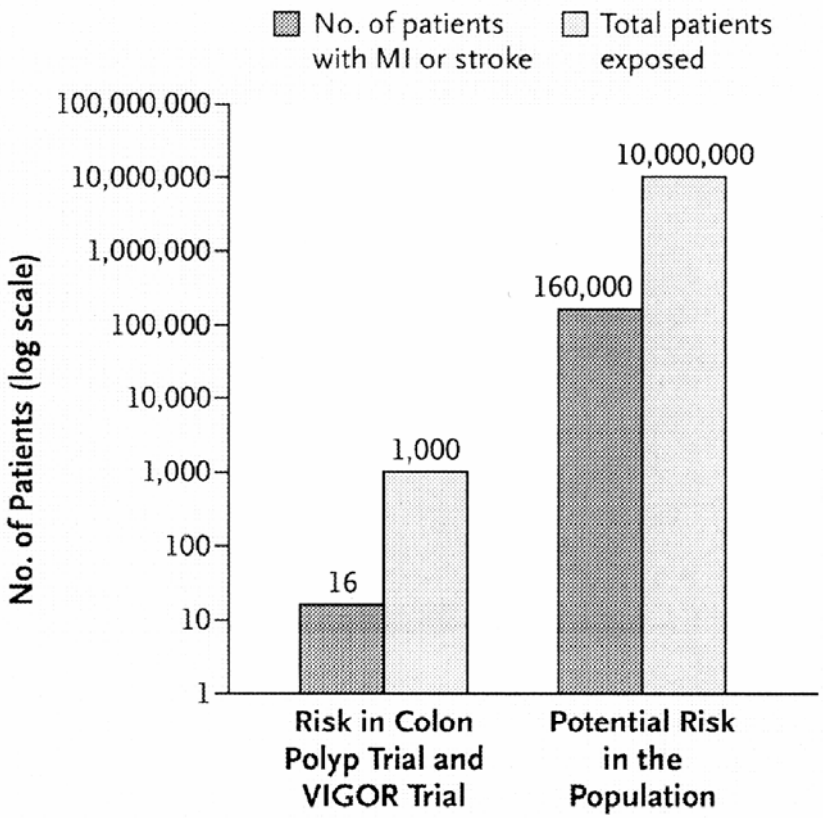
Juni et al. *Lancet*. 2004

Vioxx: 2001-4

- Several large epidemiologic studies suggest risk
- Annual sales: $1B
- Annual DTC advertising: >$100M

Vioxx: 2001-4

- Several large epidemiologic studies suggest risk
- Annual sales: $1B
- Annual DTC advertising: >$100M
- APPROVe study analysis:
  - 2600 patients (none with known CAD)
  - Incidence of MI/Stroke:
    - Vioxx – 3.5%
    - Placebo – 1.9%

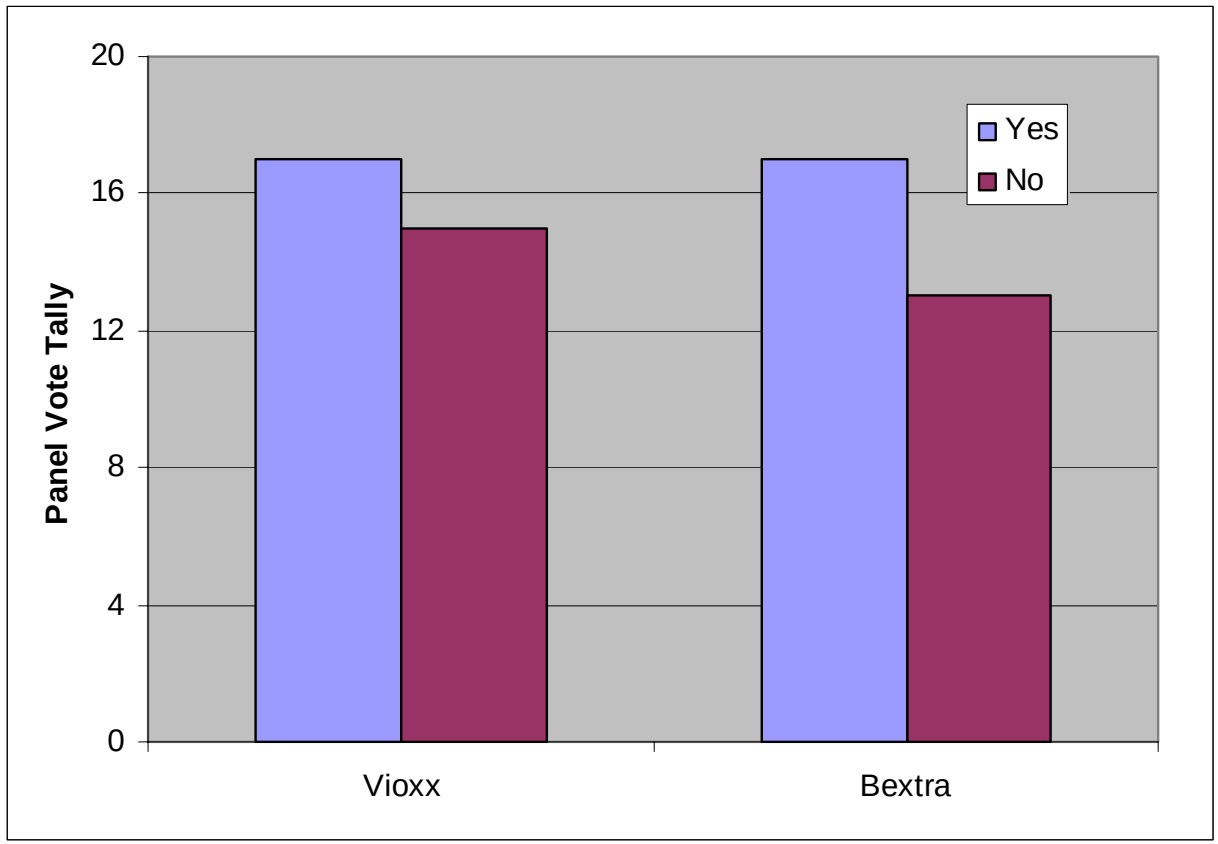


Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

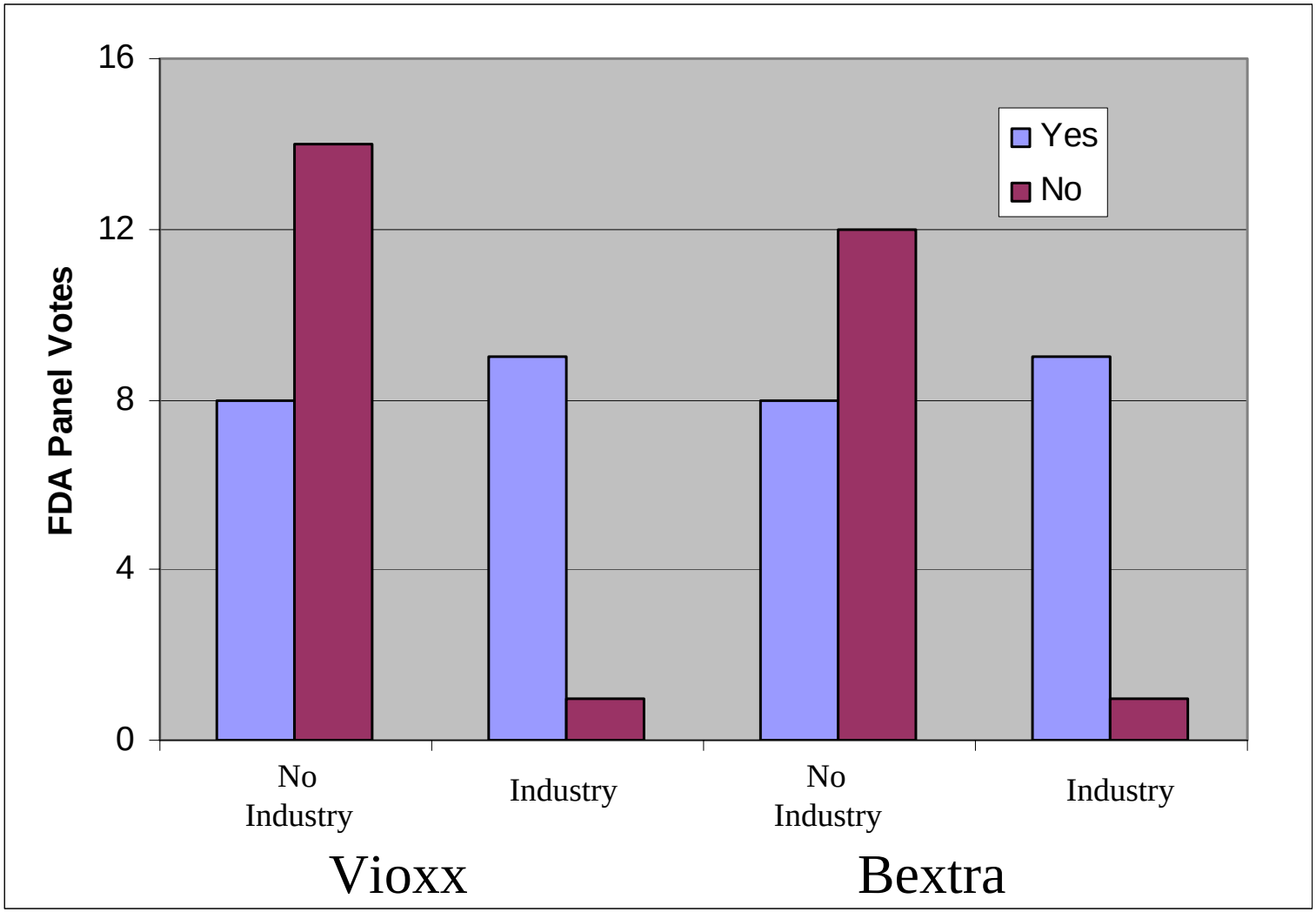
Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

Should Vioxx/Bextra be on the market?

2005 FDA Panel says……



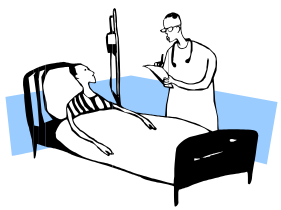
FDA Panel vote on Bextra/Vioxx vs. Industry Ties:



Bench to Bedside

Data Analysis
& Interpretation

Scientific Evidence

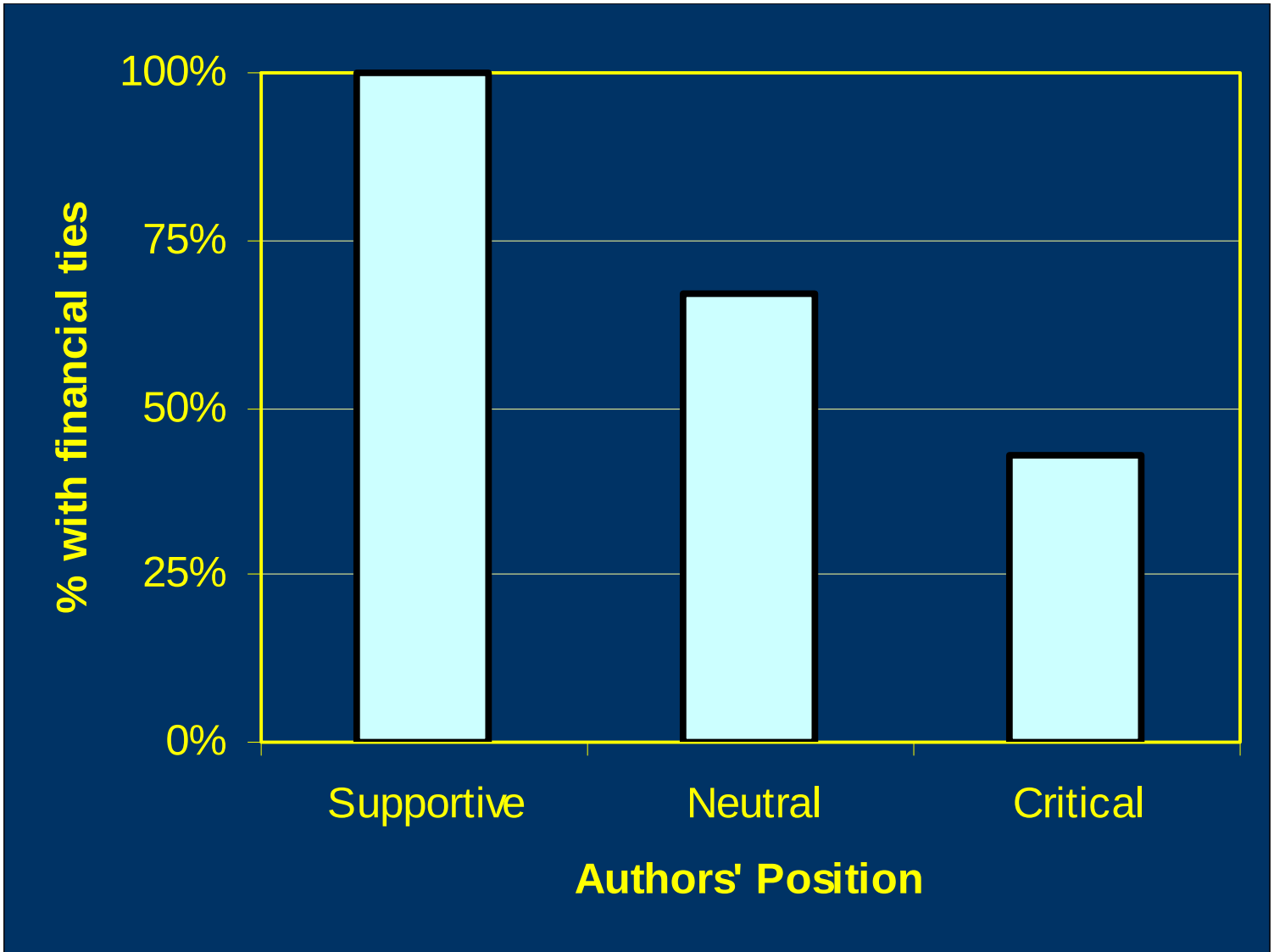


Conflicts of Interest and Interpretation

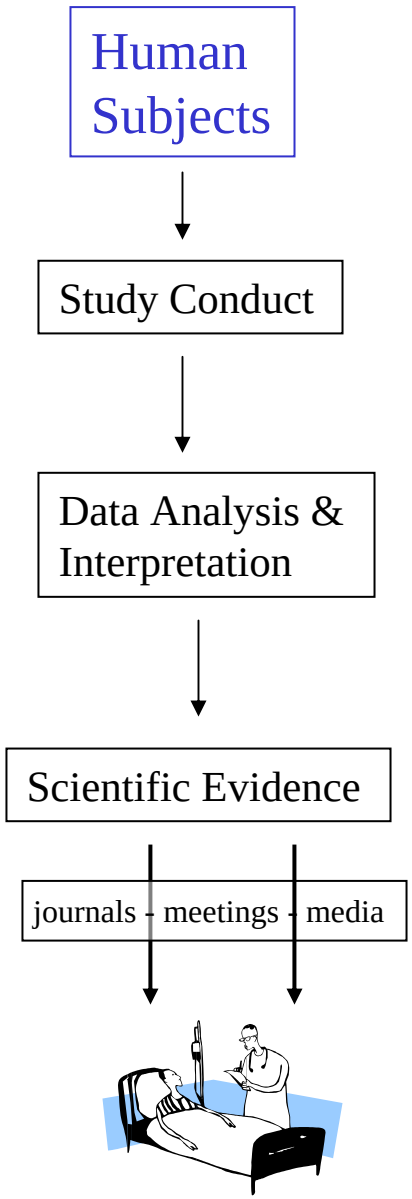
- 1995-1996 articles on the safety of Ca channel blockers.

- 70 articles
  - 5 original research papers
  - 32 reviews
  - 33 letter to the editor

Authors' published opinions were related to their financial arrangements



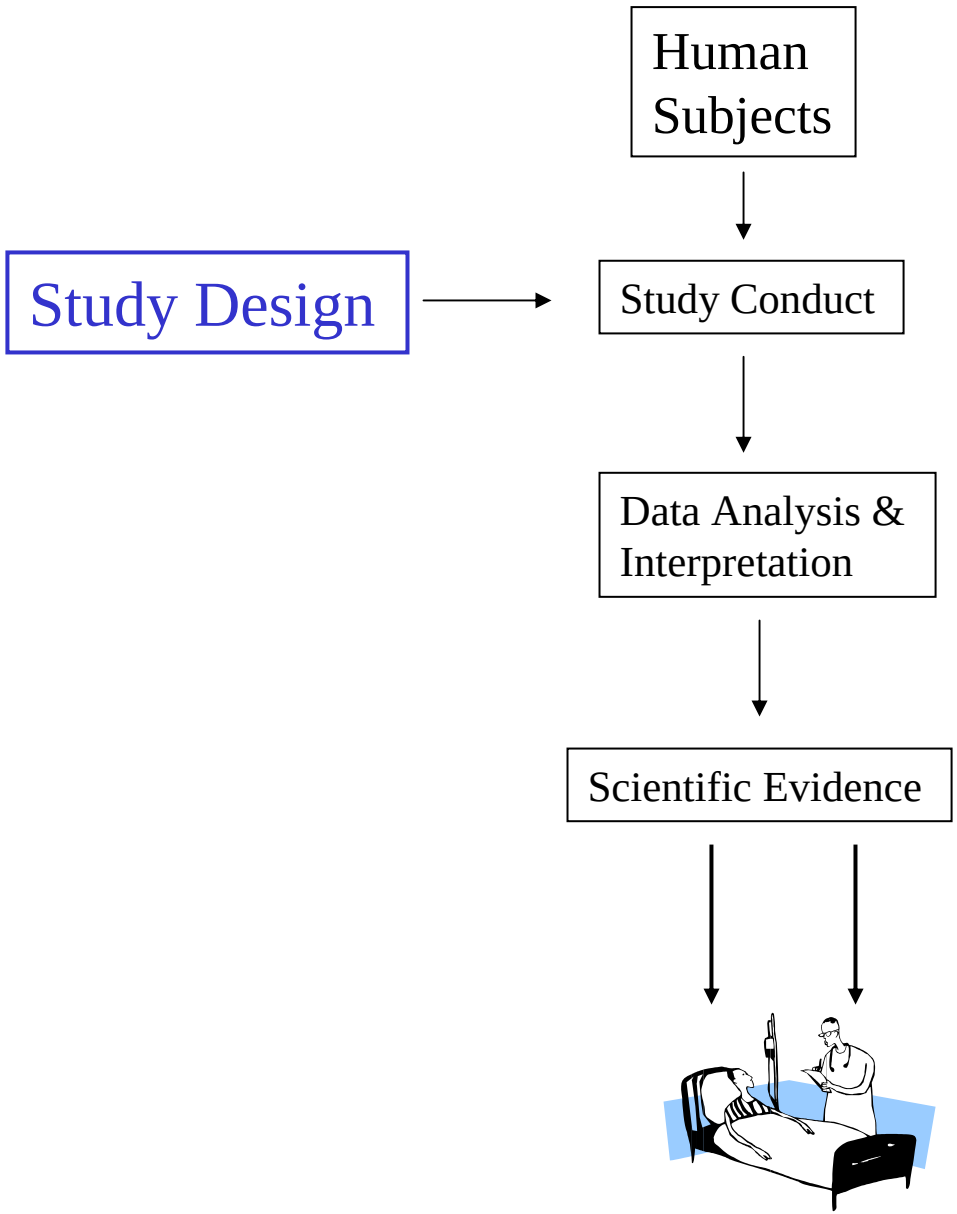
Bench to Bedside



Jesse Gelsinger case

- Phase I gene therapy trial
- Treated-related death
- FDA investigation found:
  - lapses in notifying FDA re: 4 prior adverse reactions
  - Informed consent forms changed (omitting mention of animal deaths)
  - Gelsinger's ammonia was above acceptable level
- COI - U Penn, Dr. James Wilson (PI) both had equity in Genovo, Inc.

Bench to Bedside

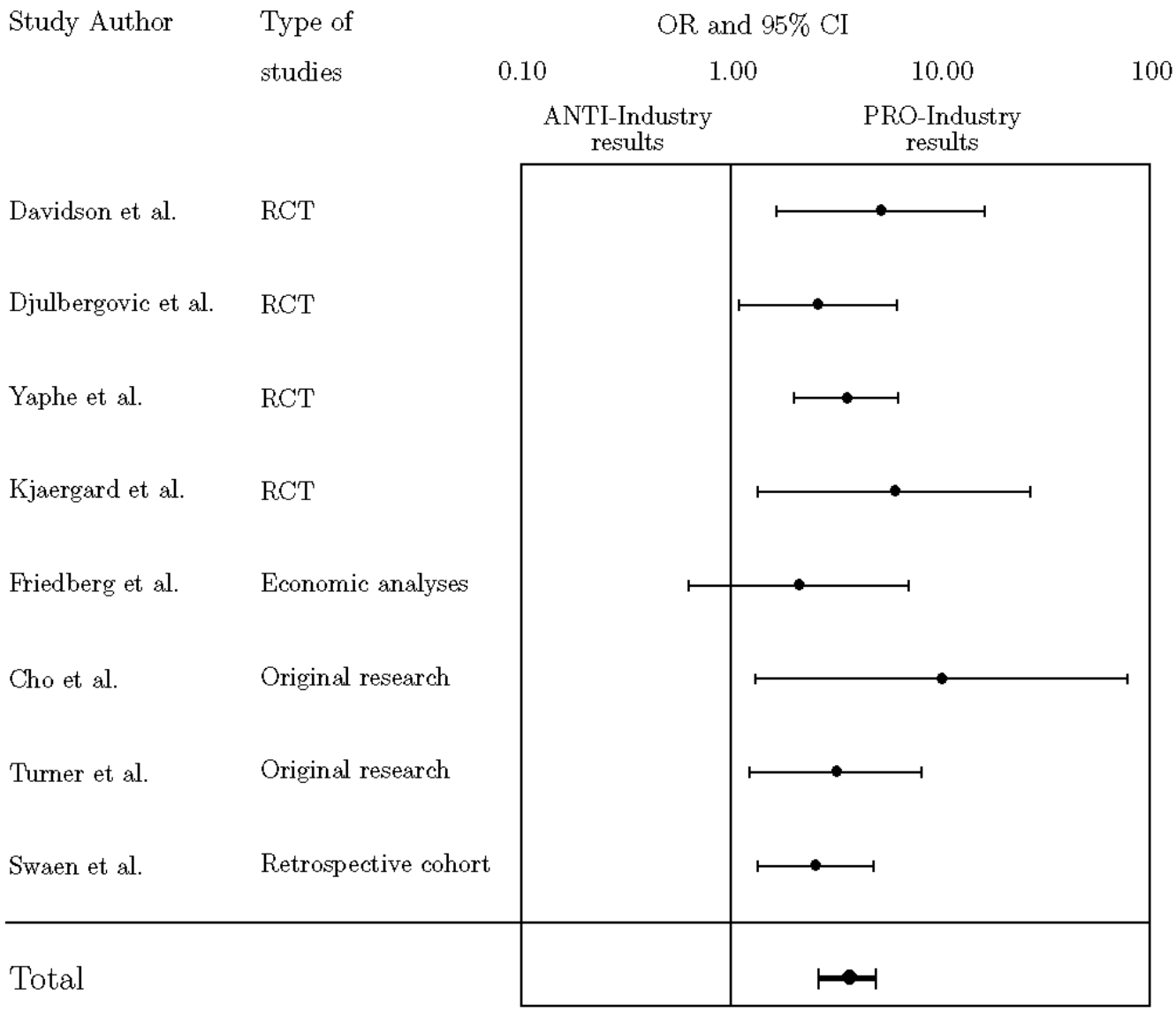


Study design bias

- Example: inferior comparison agents
- Fluconazole vs. amphotericin B
  - 92% of patients were in trials supported by the manufacturer of fluconazole.
  - *oral* amphotericin B used as comparison agent
    - poorly absorbed
    - rarely used for systemic infections
- Fluconazole looks like wonder-drug!

Johansen et al. JAMA. 282(18): 1752-1759

Systematic Review: Industry Sponsorship vs. Study Outcome



Bekelman et al. *JAMA*. 2003: 289: 454-65

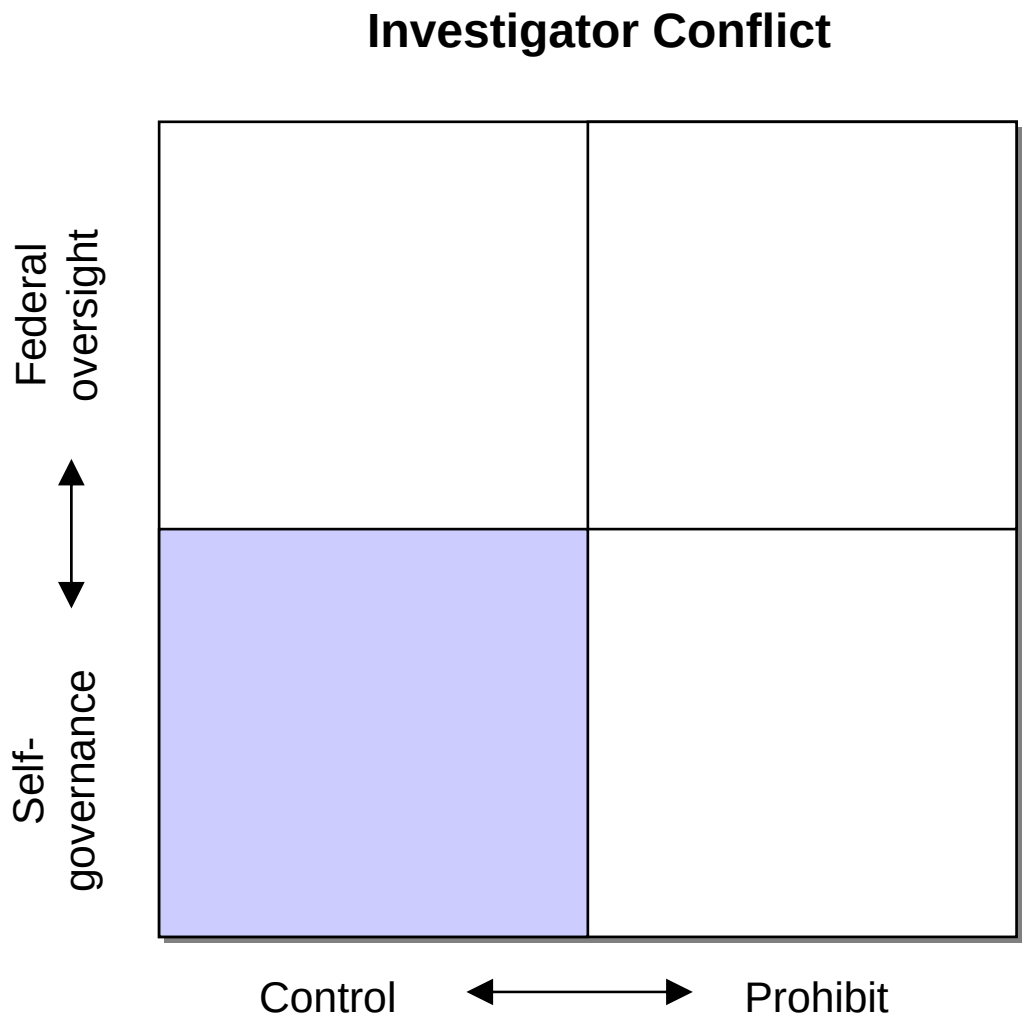
Part II Summary: Financial Conflicts in Research are….

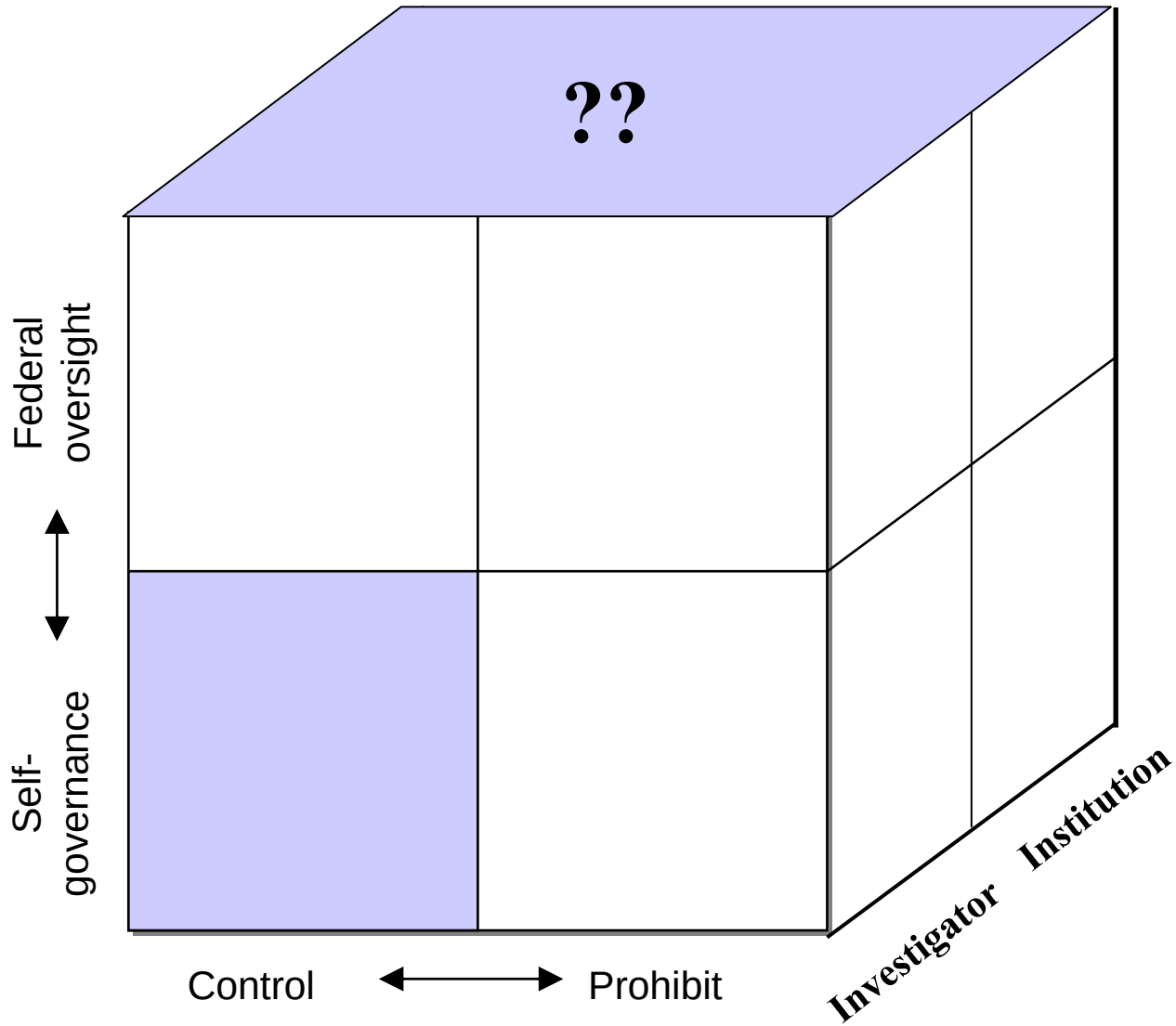
- Pervasive
- Powerful
- Clinically Hazardous
- A threat to scientific integrity

Part III: “Repairing” the Clinical Research System: Where do we go next?

- Past Approach to Managing Conflicts
- Recent developments:
  - Societies
  - Journals
  - Industry
  - Government

Addressing COI

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Federal oversight
Self-governance
Control
Prohibit
Investigator
Institution

ASCO restrictions for clinicians involved in research

- Finders fees
- Accrual bonuses
- Payment contingent upon research outcome
- Sponsor control of publication/dissemination of results.

ASCO – Restrictions on people in "leadership role"

- Stock/equity in trial sponsor
- Royalties/licensing fees
- Patents
- Position as officer/board member
- Honoraria

International Committee of Medical Journal Editors, 2001

"Editors may choose not to publish an article unless the authors":

- Have full access to study data
- Take responsibility for
  - Data integrity
  - Data analysis.
- Were free to publish results

Trial Registration

(required by ICMJE for trials starting after July, 2005)

- Hypothesis
- Interventions
- Endpoints
- Eligibility criteria
- Funding Source

ClinicalTrials.gov

Financial Conflicts at the NIH

- Prior to 2004, many NIH officials were permitted to keep consulting income confidential.
- Some high level officials, collected secondary income and stock options from biomedical companies.
- On December 7, 2003, the LA Times published an expose describing conflicts of interest among NIH employees. Some individuals reportedly collected $500K and more in consulting fees.

Willman, David. “Stealth Merger: Drug Companies and Government Medical Research.” NY Times 7 Dec. 2003.

"Conflict of Interest Information and Resources." 31 Aug. 2005. NIH. 20 Sept. 2005 <http://www.nih.gov/about/ethics_COI.htm>.

NIH Ban on Financial Conflicts

Feb, 2005

- Intramural Investigators
- Extremely Strict
  - What is Prohibited
    - Consulting
    - Speaking
    - Investments
  - Types of Entities
    - Industry
    - Hospitals
    - Insurers
    - Societies….

NIH Revised Ethics Regulations

- The top 200 NIH executives: biomedical stock holdings < $15,000.
- Roughly 6,000 other employees must submit their stock holdings for review for potential conflicts.
- NIH scientists permitted to:
  - hold fiduciary positions in medical societies
  - deliver medical education lectures paid for by drug companies.
  - Obtain outside employment involving interests unrelated to NIH duties

Gardiner, Harris. "*Health Agency Tightens Rules Governing Federal Scientists*." NY Times 26 Aug. 2005.

"Conflict of Interest Information and Resources." 31 Aug. 2005. NIH. 20 Sept. 2005 <http://www.nih.gov/about/ethics_COI.htm>.

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